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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,451	06/25/2002	John Michael Beals	X-12553	8155

7590 01/13/2006

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EXAMINER	
NOAKES, SUZANNE MARIE	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 01/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,451	BEALS ET AL.	
	Examiner	Art Unit	
	Suzanne M. Noakes, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-59* is/are pending in the application.

4a) Of the above claim(s) *33-36,44 and 46-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-42, 45 and 53-59* is/are rejected.

7)☒ Claim(s) *43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10-09-2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group II claims 37-43, 45 and 53-59 in the reply filed on October 17, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The election is therefore made FINAL.

Status of the Claims

2. Claims 37-43, 45 and 53-59 are under examination. Claims 33-36, 44 and 46-52 are withdrawn from further consideration as being drawn to non-elected subject matter.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on October 11, 2005 has been considered by the examiner. See signed and attached PTO-1449.

Claim Objections

4. Claim 43 is objected to because of the following informalities: The claim is dependent upon non-elected subject matter. The claim should be rewritten in independent form that includes the elected sequence from claim 33. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claims 54-55 recites the limitation "wherein the aldehyde polymer and the protein in the solution are present at a ratio of 0.08 to 24 on a mole polymer per mole protein basis" in reference to the preferred ratio of PEG-aldehyde to protein used in the method step of claim 53. The specification clearly states on p. 40, last paragraph, that the preferred procedure uses a molar excess of PEG-aldehyde, relative to the number of *amines present on the protein.* And that the preferred ratio is 0.08 to 24 or more preferably 1 to 10.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 37-42 and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Delgado et al. (Pharmaceutical Sciences, 1997, v.3, pp. 59-66). Delgado et al. teach non-glycosylated erythropoietin (EPO) that is pegylated with both monomethoxyPEG 5000 and (MPEG) tresylated monomethoxyPEG (TMPEG) (see p. 62, 2nd column, 1st

paragraph; and Figure 4). It should be noted that the formula of MPEG falls within the scope of the generic PEG formula in claim 37. The molecular weight/size of the PEG-aldehyde in claim 37 is determined by the number of the X components which is defined by ranges in claims 38-41. Thus the upper limit of X=1200 is equivalent to a molecular weight of 20kDa; and the lower range limit in claim 41 of X=225 is equivalent to a molecular weight of 5kDa]. Thus the limitations of the claims have been met.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 37-41, 45 and 53-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Delgado et al. as evidenced by Francis et al. (Intl. J. Hetatology, 1998, v. 68, pp. 1-18) and in view of Zilipsky (Adv. Drug Deliv. Revs., 1995, v.16, pp. 157-182) and Chamow et al. (Bioconjugate Chem. 1994, v. 5, pp. 133-140), and further in view of Eschbach (Nephol. Dialysis Transplant, 1995, v.10, supp. 2, pp. 96-109).

The teachings of Delgado et al. is cited above Section 6. It is further taught that the reasons for pegylating a protein is well known in the art and the technique provides solutions to many of the problems encountered by using non-pegylated proteins. The benefits range from increased plasma half-life, reduced immunogenicity and antigenicity, enhanced solubility, resistance to proteolysis (which will also increase the

half-life) and reduction of losses at injection sites (see Delgado et al., p. 60, 1st paragraph, 1st column). The process for pegylation is performed either by using MPEG or TMPEG, both which use a linkerless polymer attachment method. The later uses tresylated chloride and according to Francis et al., it forms a secondary amine bond between either the N-terminus or free lysine groups, or alternatively free thiols (see p. 5, 1st column, 1st paragraph). However, the method of pegylating as taught in Delgado et al. and explained further in Francis et al., proves to have low bioavailability and only suggests that the activity can be maintained *in vitro* (see Francis et al., Figures 4 and 7). Thus, Delgado et al. and Francis et al. do not teach a method of pegylating non-glycosylated EPO via a process that will be active *in vivo*.

Zalipsky teaches the chemistry behind attaching PEG molecules with biologically active molecules. It is taught that PEG is widely used as a covalent modifier of biological molecules as well as a carrier for low molecular weight drugs. An overview of 13 different reagents and methods of pegylation is reviewed. Specifically, it is taught that despite initial reports of difficulties in introducing acetaldehyde end groups by oxidation of terminal hydroxyls of commercially available MPEG's, Chamow et al. were successful in performing this task. This specific route of pegylating proteins uses sodium cyanoborohydride as the reducing agent (see Figure 2) and it is stated: "The positive attributes of this conjugation strategy are in its selectivity towards primary amino groups of proteins and formation of stable attachments of the polymer chains without change in the net charge of the protein. According to Chamow et al., the extent of protein modification with MPEG-aldehyde and sodium cyanoborohydride is easily

controlled by fine-tuning the reaction conditions and ratio of the reacting species. While this might be true for various other PEG reagents, reductive alkylation with MPEG and sodium cyanoborohydride is a relatively slow reaction and thus might be more amenable to control." The method that Zalipsky is referring to is that of Chamow et al. who teach in their abstract, that their attempts to prolong *in vivo* half-life of their desired protein was achieved by their method. The method consists of synthesizing monomethoxypoly(ethylene glycol) aldehyde and reacting the MPEG-aldehyde with the desired protein (CD4-IgG in this instance) over a variety of molar protein to MPEG ratios. The reaction was carried out at pH 7.5 for varying times at 0 and 23 °C in Hepes buffer and cyanoborohydate which serves to perform the reductive alkylation between the MPEG-aldehyde and protein which results in the formation of a secondary amine bond (see Abstract and Conjugation of MePEG to CD4-IgG on p. 135). The MPEG:protein ratio was in the range of 3-15 mole MPEG to one mole protein (see Table 2 and p. 138, last paragraph).

Eschbach teaches that recombinant human erythorpoeitin has been used successfully for almost a decade since its introduction and that many patients have benefited from its use to increase the hematocrit levels in patients suffering from anemia or dialysis patients. However, it is taught that one of the major drawbacks to this drug is that is expensive to produce.

The motivation to combine the teaching of Delgado et al. which, is a non-glycosylated EPO molecule with low bioavailability and *in vivo* activity with the method of Chamow et al. (and detailed by Zalipsky) comes from success that Chamow et al.

had on *in vivo* activity of CD4-IgG using the method they describe. One would be motivated to combine these two teachings because obviously it would be desirable to have a non-glycosylated EPO protein which can be made in bulk and cheaply by *E. coli* recombinant production, but which is also active *in vivo* (non-glycosylated EPO is inactive because it cleared from the system so quickly and can not bind to its receptors, proper pegylation would overcome this problem). The method of Chamow et al. provides a clearly defined, carefully controlled pegylation process that has proven successful in increasing the *in vivo* activity of proteins. Thus a skilled artisan would recognize the benefits of combining the two teachings which would likely produce a functional non-glycosylated, PEG-aldehyde EPO. An expectation of success in producing an active MPEG-aldehyde EPO would be likely because Chamow et al. teach in their last line, the more general implication of their results is that MePEGylation by reductive alkylation can be a useful strategy, especially for proteins in which amino groups are not critical for biological activity; and because the significant success that their method had on CD4-IgG. Furthermore, it would be obvious to use this method of making non-glycosylated pegylated EPO and use in a method to treat patients/mammals in order to increase their hematocrit levels because Eschbach teaches that this is what EPO does naturally when it is administered to mammals and also because Eschbach teaches that one of main draw backs for treating more people that are in need of increased hematocrit levels (e.g. anemia or renal dialysis patients) is because it is so expensive to produce.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a non-glycosylated, PEG-aldehyde EPO compound with a secondary amine bond between the protein and PEG molecules and furthermore to use this compound in a method to treat mammals in order to increase their hematocrit levels.

Conclusion

11. Claims 33-42, 45 and 53-59 are not allowed. Claim 42 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Noakes, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 7.30am to 4.00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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SMN
04 January 2006

JON WEBER
SUPERVISORY PATENT EXAMINER